

## **REMARKS**

In the Action, claims 1, 2, 7, 12-15 and 17-20 are rejected. In response, claim 1 is amended, and claims 2 and 12 are cancelled.

Claim 1 is amended to recite the bone formation agent being a porous pure-phase beta-tricalcium phosphate having three discrete ranges of pore size and the maxima of the discrete pore size as in original claims 2, 3 and 12. Support for the claimed feature of pure-phase beta-tricalcium phosphate is found on page 6, in the second paragraph of the specification. Accordingly, these amendments are supported by the specification and claims as originally filed.

In view of these amendments and the following comments, reconsideration and allowance are requested.

### **The Rejections**

Claims 1, 2, 7, 12-15 and 17-20 are rejected under 35 U.S.C. § 103(a) as being obvious over DE 29922585, WO 02/083194 to Beam et al. and U.S. Patent No. 6,210,715 to Starling et al. The rejection is based on the position that it would have been obvious to combine the teachings of Beam et al. and Starling et al. to modify the process and product of DE '585.

Enclosed is a Declaration by the inventor outlining various differences between the cited art and the claimed invention. The Declaration further discusses the test data demonstrating the improved and unexpected properties of the claimed bone formation agent in relation to the prior implants and bone formation agents.

The present invention as claimed is directed to a bone formation agent that exhibits several advantages over the prior bone formation agents. The bone formation agent according to the claimed invention is stable, biodegradable and avoids disintegrating into small pieces or

particles that can provoke inflammatory reactions. The bone formation agents of the cited art do not exhibit these advantages. As discussed herein, the implant materials disclosed in the cited patents are not stable and biodegradable and can provoke inflammatory reactions due to disintegration into small particles. The pore size of the prior implant materials is large in comparison to the claimed invention that can allow infections to occur.

The advantages of the claimed invention are provided by the combination of each of the features of claim 1. Specifically, the advantages are provided by (a) the bone formation agent made from porous pure-phase beta-tricalcium phosphate, (b) the three discrete pore size distribution in the range of 0.5 to 10  $\mu\text{m}$ , 10 to 100  $\mu\text{m}$ , and 100 to 5000  $\mu\text{m}$ , (c) the sintered primary particles of the calcium phosphate having a particle size smaller than 63  $\mu\text{m}$  with a  $d_{50}$  value of 5 to 20  $\mu\text{m}$ , (d) the interconnecting pore share and the porosity being limited to pore sizes less than 10  $\mu\text{m}$ , and (e) the maxima of the discrete pore size distribution of (II) and (III) having a value less than half the average granulate size of a granulate fraction in the range of 10 to 50% of the average granulate size of the granulate fraction. The art of record either standing alone or in combination does not suggest to one skilled in the art the combination of the claimed properties or the advantages of the claimed features. The Action suggests that the claimed properties are simply optimization. Applicants respectfully submit this position is based on hindsight and is not supported by the art of record. Moreover, the art of record provides no guidance to one skilled in the art to obtain the specific combination of features as recited in claim 1.

The pure-phase beta-tricalcium phosphate of the claimed invention provides a more stable bone regeneration material while maintaining biodegradability without provoking an inflammatory response. Calcium phosphate can exist in several different phases that differ in

thermodynamic stability and solubility. For example, hydroxyapatite is thermodynamically stable and the most insoluble form. However, hydroxyapatite is not biodegradable due to its stable and insoluble characteristics. The phase transitions are dependent on both time and temperature and can readily occur during the sintering process. The different phases also have a different volume and thermal expansion coefficient so that overstressing and cracking can occur in the microstructure of mixed phase calcium phosphates. The art of record does not recognize these advantages and provides no suggestion to one skilled in the art to use a pure-phase beta-tricalcium phosphate.

The pure-phase beta-tricalcium phosphate, the three discrete pore size distributions, the sintered primary particles and particle size and the maxima of the discrete pore size distributions as claimed provide for full biodegradation. In particular, the maxima of the discrete pore size distribution as claimed provides a uniform specific surface which results in a constant material to solution ratio and a homogenous resorption. This feature is demonstrated by Figure 1 in the enclosed Declaration.

The pure-phase beta-tricalcium phosphate, three discrete pore size distributions, sintered primary particles and particle size in the maxima of the discrete pore size distribution also provide improved osteointegration and osteoconductivity.

Heterogeneous materials that are not made from a pure-phase beta-tricalcium phosphate as in the claimed invention decompose into small particles which trigger inflammatory reactions as a result of the chemical degradation and biological resorption. The small particles inhibit osteoconduction since fibrous tissue can grow into the defects and prevent bone healing. Materials that are highly stable such as hydroxyapatite are not fully reabsorbed.

The bone formation agent of the claimed invention is mechanically stable and has a high porosity as a result of the combination of each of the claimed features noted above. The improved mechanical stability is primarily due to the combination of the three discrete pore sizes, the sintered primary particles and particle size, and the interconnecting pore share being limited to less than 10  $\mu\text{m}$ . The improved stability prevents decomposition into smaller subparticles and reduce the risk of inflammatory reactions.

The interconnecting pore share having pore sizes less than 10  $\mu\text{m}$  prevents the invasion of germs into the macropores as disclosed on page 8, second paragraph, and page 9, third paragraph, of the present specification. Infection which ultimately leads to the loss of the implant is a common problem in the prior synthetic ceramics. The bone formation agent of the present invention avoids this disadvantage of the prior products.

The enclosed Declaration demonstrates the advantages of the claimed bone formation agent compared to the prior bone implants. The data discussed in the Declaration demonstrates that the combination of each of the features noted above provides enhanced mechanical stability and improved bone regeneration as a result of the claimed interconnective open multiporosity and the granule size and structure. In particular, the data demonstrates that the three discrete pore size distributions and the interconnecting pore share having a pore size less than 10  $\mu\text{m}$  provide improved mechanical stability and improved bone regeneration. The sintered primary particles having a particle size smaller than 63  $\mu\text{m}$  and a  $d_{50}$  value of 5 to 20  $\mu\text{m}$  provide the improved granule size and structure. The three discrete pore size distributions produce an enhanced capillary effect that ensures cell nutrition and resorption from within the granules. In addition the material is fully resorbed and does not degrade or disintegrate into small particles

that can provoke inflammatory reactions. The pore size distributions and interconnecting pore size also reduce the risk of infections that commonly occur in the prior products.

The art of record does not disclose or suggest the combination of these features. DE '585 does not disclose or suggest the three discrete pore size distributions, a sintered primary particle having a particle size smaller than 63  $\mu\text{m}$ , interconnecting pore share with pore sizes less than 10  $\mu\text{m}$  or a maxima of the discrete pore size distribution as defined in claim 1. As discussed above and in the enclosed Declaration, the combination of these features is important to achieve the advantages and effects of the claimed bone formation agent. For example, the claimed sintered primary particles having a particle size small than 63  $\mu\text{m}$  provides a strong ceramic bond in the sintered particles to the stable sintering necks that provide an additional benefit in preventing inflammatory reactions.

DE '585 discloses a temporary bone defect filler having microporous and macroporous structures. The micropores make up 10 to 50% and the macropores make up 50 to 90% of the total porosity. DE '585 has partially interconnecting macropores that make up 50 to 90% of the total porosity and non-interconnecting adjacent macropores connected by the cell walls by micropores. DE '585 does not disclose or suggest the features of the claimed invention.

Beam et al. does not provide the deficiencies of DE '585. Beam et al. relates to engineered regenerative biostructures having resorbable regions and non-resorbable regions. The structure according to Beam et al. contains hydroxyapatite as disclosed on page 2, lines 24 and 26, macropores having a medium pore size between 10 and 15  $\mu\text{m}$  and interconnecting mesoporosity and/or microporosity. As discussed above, the hydroxyapatite of Beam et al. is not biodegradable as in the claimed invention.

Beam et al. demonstrates that the biodegradation products of some materials can activate inflammatory responses and that coordinating the porosity and internal architecture of the structure to specific responses has not been attained. Thus, one skilled in the art would recognize based on Beam et al. that even minor modifications in the choice of the specific calcium phosphate including its purity, pore size distribution, porosity, particle size and particle shape are critical factors that influence the properties and characteristics of the final material.

Beam et al. also fails to disclose or suggest the combination of the claimed use of porous pure-phase beta-tricalcium phosphate, the three discrete pore size distributions, the sintered primary particles having a particle size smaller than 63  $\mu\text{m}$ , the interconnecting pore share and the maxima of the discrete pore size distribution as recited in claim 1. Thus, Beam et al. in combination with DE '585 does not suggest to one skilled in the art the claimed invention.

Starling et al. also fails to provide the deficiencies of DE '585 either alone or in combination with Beam et al. The Action on page 4 suggests that the interconnecting pores and size are "routinely altered by changes in sintering temperature as taught by Starling". For the reasons discussed below, Starling et al. does not lead one of ordinary skill in the art to attain the claimed invention.

Starling et al. relates to hollow calcium phosphate microbeads or microspheres for use in cell culturing systems, chromatography and implantable biomedical materials. The calcium phosphate microspheres of Starling et al. for chromatographic applications have a particle size of about 10  $\mu\text{m}$  to 100  $\mu\text{m}$  with open porosity in the range of 20% to 60% and a pore size range of about 0.01 to about 0.5  $\mu\text{m}$ .

Starling et al. discloses the microspheres for use as biomedical implants having a size range of 500 to 1000  $\mu\text{m}$  and an interstitial open porosity of about 60% with a pore size range of 350  $\mu\text{m}$  to 500  $\mu\text{m}$ . See, for example, column 8, line 58, to column 9, line 1, of Starling et al.

Changing the sintering temperature is not routine optimization as suggested in the Action. One skilled in the art would readily recognize that changes in sintering temperature would result in a heterogeneous material due to phase transitions and would result in a collapse of the pores so that the final product would lack the pore size distributions as presently claimed. Modifying the sintering temperature as suggested according to the Action would result in a dense product of mixed calcium phase phosphates that does not possess the claimed pure-phase beta-tricalcium phosphate, the porosity or pore size distribution. As demonstrated in the attached Declaration, modifying DE '585 according to the suggestion in the Action to change the sintering temperature and time would produce a highly closed porosity composition with fewer and smaller interconnecting pores that are not resorbable. Thus, modifying the sintering temperature is not a routine change in the art as suggested by the Examiner and would not inherently produce the claimed invention. One skilled in the art in reviewing Starling et al. would have no reasonable expectation of success in attaining the claimed invention simply by modifying the sintering temperature as suggested by the Examiner.

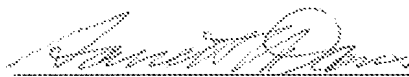
Starling et al. does not disclose or suggest pure-phase beta-tricalcium phosphate, the claimed three discrete pore size distributions, an interconnecting pore share in the porosity limited to pore size less than 10  $\mu\text{m}$ , or the maxima of the discrete pore size distributions of (II) and (III) are a value less than half the average granulate size of a granulate fraction and in the range of 10 to 50% of the average granulate size.

DE '585, Beam et al. and Starling et al. specifically teach large interconnecting meso- and/or macropores as an essential feature. In contrast, the claimed invention does not exhibit interconnecting mesopores and macropores. The claimed pore sizes would not be attained based on the teachings of Starling et al. either alone or in combination with DE '585. Modifying the sintering temperature according to Starling et al. as suggested in the Action would result in a dense material that is not resorbable, and thus, not suitable for use as bone formation agents.

In view of the above comments, the claims are submitted as being allowable over the art of record. The dependent claims are also allowable as depending from an allowable base claim and for reciting additional features of the invention. The art of record does not disclose the volume shares of the discrete pore size distributions as in claim 4, the phase purity of the beta-tricalcium phosphate of claim 6, the particle size range of the granulate fractions of claim 7, the geometric shapes of claims 8, 9 and 10, the shaped body of claim 13, the statistical porosity of claim 14, the tubular porosity and diameter range of 0.5 to 2 mm of claim 15, the compact shaped body of claim 16, the substances on the surface and/or internal pore structure of claim 17, and the shape of the bone formation agent of claims 18-20, in combination with the features of claim 1. Accordingly, these claims are submitted as being allowable over the art of record.

In view of these amendments, reconsideration and allowance are requested.

Respectfully submitted,

  
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